Associations between measures of structural morphometry and sensorimotor performance in individuals with non-specific low back pain

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Abbreviations:

NSLBP = non-specific low back pain

STSTS = sit-to-stand-to-sit

ABSTRACT

Background and Purpose: So far, the majority of the structural brain imaging studies in non-specific low back pain (NSLBP) evaluated volumetric changes. Although it is suggested that specific measures such as cortical surface area and cortical thickness reflect different underlying neural architectures, the literature regarding these different measures in NSLBP is limited. Therefore, the current study was designed to investigate the association between the performance on a sensorimotor task, more specifically the sit-to-stand-to-sit (STSTS) task, and cortical surface area and cortical thickness in individuals with NSLBP and healthy controls.

Materials and Methods: Seventeen individuals with NSLBP and 17 healthy controls were instructed to perform five consecutive STSTS movements as fast as possible. In addition, T1-weighted anatomical scans of the brain were acquired and analyzed with Freesurfer.

Results: Compared to healthy controls, individuals with NSLBP needed significantly more time to perform five STSTS movements ($p < 0.05$). Furthermore, lower STSTS performance on unstable support surface was associated with decreased cortical thickness of the rostral anterior cingulate cortex in individuals with NSLBP and healthy controls ($r = -0.47$, $p < 0.007$). Brain morphometric analyses revealed that cortical thickness of ventrolateral prefrontal cortical regions was increased in patients with NSLBP when compared to controls. Also, a positive correlation was found between perceived pain intensity and cortical thickness of the superior frontal gyrus ($r = 0.70$, $p < 0.002$) and the pars opercularis of the inferior ventrolateral prefrontal cortex ($r = 0.67$, $p < 0.004$). Hence, increased cortical thickness was associated with increased levels of pain intensity in the individuals with NSLBP. No associations were found between cortical surface area and the pain characteristics in this group

Conclusion: The current study suggests that cortical thickness may contribute to different aspects of STSTS performance and perceived pain intensity in the NSBLP population.

INTRODUCTION

Non-specific low back pain (NSLBP) refers to low back pain that is not attributable to a specific cause. This category of low back pain disorders includes the majority of all low back pain complaints[1-3]. Despite many efforts in the development of treatment strategies for this large population[4], effects of current NSLBP interventions are rather small. Therefore, understanding the underlying neural basis of NSLBP is crucial.

Previous imaging studies showed structural alterations in (sub)cortical brain regions in individuals with NSLBP. However, mixed findings were obtained. Both increases and decreases in gray matter volume in different brain regions were found in individuals with NSLBP compared to healthy controls. Volumetric alterations in individuals with NSLBP were observed for example in the dorsolateral prefrontal cortex[5-7], in the somatosensory cortex[6,8,9], in the temporal lobes[6,8] and in the thalamus[5-7]. Together, the majority of gray matter alterations in NSLBP, either reduced or increased, are observed in areas related to sensorimotor control. These alterations in sensorimotor related areas are indicative of impaired sensorimotor performance, as observed in individuals with NSLBP using behavioral measures[10-12]. For example, individuals with NSLBP need significantly more time to perform five consecutive sit-to-stand-to-sit (STSTS) movements compared to healthy controls[13]. This STSTS task necessitates optimal sensorimotor control, which requires an efficient processing of sensory and motor information across the brain[14]. However, nearly all structural brain imaging studies in NSLBP and in sensorimotor control evaluated volumetric changes. Only one study in patients with Parkinson's disease investigated how structural morphometry was associated with motor performance, showing an association between cortical thinning of the sensory parieto-temporal areas and motor deficits[15]. However, in NSLBP cortical thickness and cortical surface

area have been relatively understudied, while these two aspects of brain structure may be crucial to functional connectivity.

Cortical thickness and cortical surface area have a distinct genetic origin[16,17], a contrasting phylogeny[18] and different developmental trajectories[19]. In addition, it is suggested that cortical thickness and cortical surface area reflect different aspects of the underlying neural architecture[20]. More specifically, cortical surface area is primarily determined by the number of columns within a cortical region, whereas cortical thickness is thought to reflect the number of cells within these cortical columns[18,21]. Therefore, evaluation of cortical surface area and cortical thickness as separate measures can provide interesting additional knowledge on the neural mechanisms of NSLBP and sensorimotor tasks. These measures of structural morphometry can be computed by a surface-based analysis method called Freesurfer[22].

By using the Freesurfer analysis suite, two recent studies[23,24] provided evidence for alterations in cortical thickness in individuals with NSLBP compared to healthy controls. Although, Kong et al. (2013) found increased cortical thickness in the bilateral primary somatosensory cortex, somatotopically associated with the lower back, in individuals with NSLBP, Dolman et al. (2014) demonstrated that the differences in cortical thickness between individuals with NSLBP and healthy controls disappeared when controlling for age. Nevertheless, little research has been done on the associations with sensorimotor control and pain using both surface area and cortical thickness. Therefore, this study was designed to investigate the distinct relation between the STSTS performance, and the cortical surface area and cortical thickness in individuals with NSLBP and healthy controls. An association between cortical thinning of sensorimotor brain areas and a longer duration to perform five consecutive STSTS movements was hypothesized. This correlation analysis was performed to reveal the potential different contribution of the two non-volumetric

parameters to sensorimotor control. In addition, considering recent findings[23,24], we hypothesized subtle cortical thinning in both sensorimotor- and pain-related brain regions in individuals with NSLBP compared to healthy controls.

METHODS

Participants

Thirty-four subjects were studied, which included seventeen subjects with NSLBP (11 women and 6 men) and 17 age-matched (± two years) healthy individuals (12 women and 5 men). Six left-handed (2 patients with NSLBP and 4 healthy controls) were included in the study. Data from the same cohort were previously reported[25,26]. Subjects with NSLBP were recruited consecutively from 2012-2013, as they responded to flyers in various settings, i.e. academic (University Hospital Leuven) or community (sport clubs), physician referrals (speciality care), mailings and internet. Subjects with NSLBP were included if they (1) were between the ages of 20 and 50 years, (2) had experienced at least six months of disabling NSLBP (Oswestry Disability Index, version 2 (adapted Dutch version) (ODI-2)[27] > 12%), (3) were not taking heavy opioids or drugs, (4) did not have vestibular and/or self-reported specific balance problems that precluded participation in the study procedure, (5) had no previous history of brain injury or other neurological disorders, (6) had no neck problems (Neck Disability Index[28] < 6%), (7) had no previous major trauma and/or surgery of the spine or lower limbs, and (8) they met the standard "MR safe" bench test criteria (e.g., no claustrophobia, no metal implants in body). All participants gave their written informed consent prior to the study. The study conformed to the principles of the Declaration of Helsinki (1964) and its later amendments, was approved by the local Ethics

Committee of Biomedical Sciences, UZ KU Leuven, Belgium (s53802) and was registered at www.clinicaltrails.gov with identification number NCT01540617.

Description of measures

Pain characteristics

The pain characteristics are defined by the numerical rating scale (NPRS) back pain scores, scores on the ODI-2 and the number of years of NSLBP. The NPRS back pain scores (0 (no pain) to 10 (worst pain)) during the last month and at the moment of testing were reported. These scores are well validated measures to define the intensity of NSLBP[29].

Sit-to-stand-to-sit task

The equipment, paradigm parameters and dependent variables of the STSTS task were identical to previous studies[13,26]. The participants were instructed to sit barefoot on a stool that was placed on a six-channel force plate (Bertec Corporation, OH, USA) with their arms relaxed along their body and their vision occluded by means of non-transparent goggles. The stool height was adjusted for each participant to assure an angle of 90 degrees in both hips and knees. After 15 seconds of usual sitting (no instructions on posture were given), participants were asked to perform five consecutive STSTS movements, with a full range of motion and as fast as possible. An investigator stood near the participant to prevent actual falls. The force plate registered anterior-posterior center-of-pressure displacements. The center-of-pressure displacements were sampled at 500 Hz using a Micro1401 data acquisition system and Spike2 software (Cambridge Electronic Design, UK). This protocol was performed both with the feet placed on a stable (force plate itself) and on an unstable support surface (50 cm length x 41 cm width x 6 cm thickness, Airex balance pad elite) on the force plate. The total duration of the five consecutive STSTS movements was

calculated based on the anterior-posterior center-of-pressure displacement. The starting- and end-point of the task were defined by the mean value of the center of pressure during usual sitting before and after the task. The STSTS has showed good test-retest reliability (Intraclass Correlation Coefficient: ICC=0.84-0.94).[31,32]

DASS-21

Finally, a short version of the Depression Anxiety Stress Scales (DASS-21) questionnaire was administered.[32] This is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress. Subjects are asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week. Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items.

MRI acquisition and analysis

MRI images were acquired with a Philips 3 Tesla Achieva scanner (Philips, Best, The Netherlands) equipped with a 32-channel standard head coil. High-resolution whole brain T1-weighted anatomical scans were obtained with a 3D-TFE sequence (voxel size of 0.98x0.98x1.2 mm^3, repetition time of 9.59 ms, echo time of 4.6 ms, a flip angle of 8^o, 182 coronal slices, field of view of 250x250x218 mm^3 and a matrix of 256x256 mm^2). All T1-weighted anatomical scans were checked by a radiologist to assure that no brain lesions were present.

The structural images were analyzed with the Freesurfer analysis suite, which is documented and freely available for downloading online (http://surfer.nmr.mgh.harvard.edu/). Technical description of the Freesurfer procedures can be found in previous publications[33-42]. The whole-brain analysis was performed with use of additional computing resources from the high

performance computing TIER1 cluster at the University of Ghent (http://ugent.be/hpc/). The Freesurfer analysis suite is a multi-step procedure which consists of (1) removal of non-brain tissue using a hybrid watershed/surface deformation procedure (skull stripping)[42], (2) automated transformation to Talairach space, (3) subject specific parcellation of the subcortical white matter and deep gray matter volumetric structures[36,43], and (4) calculation of cortical surface area and cortical thickness from all vertices within the 34 cortical parcellations per hemisphere[44]. Results for each subject were carefully visually inspected to ensure the accuracy of the skull striping, segmentation and cortical surface reconstruction. Where needed, the appropriate manual corrections were performed as explained by the FreeSurfer Tutorial (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial). In some datasets, it appeared that the skull strip left a lot of dura. However, it did not affect the surfaces following the gray and white matter borders. The averaged values across hemispheres were calculated and used in the statistical analysis to reduce the number of comparisons.

Statistical analysis

Unpaired t-tests were used to calculate group differences in characteristics of the participants. Differences in STSTS performance were analyzed with a 2 x 2 repeated measures ANOVA with group as between-subject factor (NSLBP group and healthy control group) and surface as within-subject factor (stable support surface and unstable support surface). The significance level for group differences in characteristics and STSTS performance was set at $p < 0.05$. Multivariate analysis of covariance (MANCOVA) was used to contrast cortical thickness and surface area measurements from each cortical parcellation by group while controlling for age. Bonferroni was applied to correct for multiple comparisons resulting in an adjusted p-value of $p < 0.001$ (0.05/34) for group differences in structural morphometry. Also, for each cortical

parcellation, from the morphological measurement differences between groups, we also conducted post hoc power analyses using GPower version 3.1.9.2 (with power (1 - β) set at 0.80 and $\alpha = 0.05$, two-tailed) to determine if negative findings could be attributed to limited sample size. The outliers labeling rule (with a g-factor of 2.2)[45] was applied to detect outliers from both the STSTS data and the structural morphometry parameters. These values were excluded pairwise from the correlation analysis. Relationships between STSTS performance and pain scores on one hand and characteristics of morphometry on the other hand were examined using partial (controlling for age) Pearson correlations across the total group on the one hand and within each of the groups on the other hand (individuals with NSLBP and healthy controls), in regions with significant group differences only. The p-values reported for correlations were uncorrected for multiple comparisons with a statistical threshold of $p < 0.01$. These analyses, while showing a consistent trend, should be considered exploratory. The statistical analysis was performed with SPSS 22.

RESULTS

Characteristics of the participants

In accordance with the inclusion criteria, individuals with NSLBP reported scores above zero on the parameters of NSLBP-related disability and pain intensity (ODI-2, $NPRS_{back}$ usual and $NPRS_{back}$ current), whereas all healthy individuals scored zero on these parameters (Table 1). No significant differences in demographic characteristics were found between the individuals with NSLBP and healthy controls ($p > 0.05$), except for weight (Table I). According to the cutoff scores of the DASS-21, 3 individuals with NSLBP showed moderate to severe depression, 4 individuals with NSLBP showed moderate to severe anxiety and 5 individuals with NSLBP showed moderate

to severe stress, whereas all controls scored 0 on the three scales of the DASS-21. Six left-handed (2 patients with NSLBP and 4 healthy controls) were included in the study; however, the removal of left-handed participants did not change the results.

Sit-to-stand-to-sit task

A significant main effect of the factors 'group' ($F = 11.348$, $p = 0.002$) and 'surface' ($F = 6.29$, $p = 0.017$) was observed in the duration to perform five consecutive STSTS movements. More specifically, individuals with NSLBP needed significantly more time to perform the STSTS task on stable and unstable support surface (stable: 18.1 ± 6.9 s; unstable: 16.8 ± 5.9 s) compared to healthy controls (stable: 12.9 ± 2.5 s; unstable: 11.5 ± 2.0 s) ($p = 0.002$). Moreover, a significant decrease in duration of the STSTS task was found on unstable support surface compared to the stable condition, irrespective of group ($p = 0.017$). No interaction-effect between the factors 'group' and 'surface' was present ($p > 0.05$).

Control analyses with weight

Our results revealed a significant positive correlation between the number of years of NSLBP and weight, $r = 0.357$, $p < 0.05$. Only marginal significant correlations ($p's < 0.10$) between weight and the other measures of pain could be demonstrated (see Table 2). Also, weight of the participants was not significantly correlated with the total time needed to perform the STSTS task on stable and unstable support surface, neither with the structural morphometry ($p > 0.05$). Therefore, weight was not included in the subsequent analysis.

Structural morphometry

MANCOVA of the cortical parcellations between subjects with NSLBP and healthy controls (see Tables 3 and 4, Figure 1), including age as covariate in the model, showed cortical thickening in the individuals with NSLBP in the pars opercularis and pars triangularis of the inferior ventrolateral prefrontal cortex (p_{corr}*'s* < 0.001). These brain regions did hold significance after correcting for multiple comparisons. Using a less stringent threshold of $p < 0.01$ (indicated in cursive in Table 3), a cortical thickening trend in the NSLBP group was observed in the cuneus ($p < 0.003$), fusiform gyrus ($p < 0.004$), inferior parietal gyrus ($p < 0.002$), lateral orbitofrontal cortex ($p < 0.004$), posterior ($p < 0.008$) cingulate gyrus, superior frontal gyrus ($p < 0.01$), superior temporal gyrus ($p < 0.006$), and transverse temporal gyrus ($p < 0.004$); and a cortical thinning trend in the rostral anterior cingulate gyrus ($p < 0.009$) and the insula ($p < 0.002$).

Within these regions, we checked for correlations to depression, anxiety, and stress (as measured by the DASS-21) to exclude the possibility that the significant group differences in cortical thickness may be explained by differences in emotional states. Only one significant positive correlation within the patient group between the Depression Scale and cortical thickness was observed for the superior temporal gyrus ($r = 0.66$, $p < 0.007$).

No significant differences in cortical surface area between individuals with NSLBP and healthy controls could be demonstrated (*p's* > 0.05, Table 4). Table 4 also displays the sample sizes required to find statistically significant differences in surface area between the groups for each cortical parcellation. The numbers needed per group range from 41 to 29790. These results showed that sample size would have to increase up to at least 41 for surface area measurements, in order for group differences to reach statistical significance at the .05 level. Thus, it is likely that our negative findings for surface area can be attributed to a limited sample size.

Association between cortical thickness and the sit-to-stand-to-sit performance

Relationships (corrected for age) between STSTS performance and cortical thickness were investigated in regions with significant group effects. The duration to perform five consecutive STSTS movements on unstable support surface was negatively correlated with the cortical thickness of the rostral anterior cingulate (r = -0.47, p < 0.007) within the total group (Figure 2). In other words, a longer duration of the STSTS task on unstable support surface (lower performance) was associated with a decreased cortical thickness of the rostral anterior cingulate cortex. To some extent, this correlation coefficient between cortical thickness and STSTS performance was valid only for the NSLBP group (r = -0.51, p = 0.055)

Association between structural morphometry and pain characteristics

Within the group of individuals with NSLBP, significant positive correlations (as shown in Figure 2) were found between the NPRS back pain score (indexed by the NPRS back usual) and the cortical thickness of the superior frontal gyrus (r = 0.70, p < 0.002) and the pars opercularis of the inferior ventrolateral prefrontal cortex (r = 0.67, p < 0.004). In other words, increased level of pain intensity in the individuals with NSLBP was associated with increased cortical thickness of superior frontal gyrus and the pars opercularis of the inferior ventrolateral prefrontal cortex. It is important to note that no significant correlations were found between cortical surface area and the pain characteristics in this group of individuals with NSLBP.

DISCUSSION

Our study is the first study correlating structural morphometrics with STSTS performance in patients with chronic pain, more specifically NSLBP. Brain morphometric analyses revealed that cortical thickness of ventrolateral prefrontal cortical regions was increased in patients with

NSLBP when compared to controls. This increased cortical thickness was positively correlated with increased pain scores in the NSLBP group. Our behavioral results showed that individuals with NSLBP needed significantly more time to perform five consecutive STSTS movements on stable and unstable support surface. In addition, lower STSTS performance on unstable support surface was associated with decreased cortical thickness of the rostral anterior cingulate cortex.

Increased cortical thickness in ventrolateral prefrontal cortical regions: association with pain intensity

Numerous studies using voxel-based morphometry (VBM) have examined alterations of gray matter densities within specific brain regions in chronic pain conditions (for meta-analyses, see Pan et al., 2015; Smallwood et al., 2013).[46,47] However, surface-based features, such as cortical thickness and surface area, are more direct measures of cortical morphometry than the gray matter density values used in VBM.[34,48] To our knowledge, no study to date has examined these two measures in a group of chronic pain. So far, only two studies investigated cortical thickness in individuals with NSLBP using the Freesurfer analysis suite. One study demonstrated an increased cortical thickness of the primary somatosensory cortex, more specifically the area somatotopically representing the lower back.[23] In another study, group comparisons revealed cortical thickening in the right rostral middle frontal gyrus and a trend toward cortical thickening in the right paracentral lobule in patients with chronic low back pain. These regions did not retain significance after correcting for age. These previous findings of cortical thickening comport with our results. Our analyses, after correcting for age, revealed cortical thickening in the individuals with NSLBP in the pars opercularis and pars triangularis, which together form the mid-portion of the ventro-lateral prefrontal cortex. The changes identified in the ventrolateral prefrontal cortical regions in our group of subjects with NSLBP have face validity. That is, these brain regions appear to play an important

role in the cognitive regulation of pain and emotion.[49,50] Several VBM studies have identified changes in the ventrolateral prefrontal cortex in patients with other chronic pain conditions, such as migraine.[51,52] Experimental pain studies using functional imaging techniques have also demonstrated altered activation of the same brain regions.[53] The ventrolateral prefrontal cortex has also been reported to be involved in patients who suffer from anxiety, depressive symptoms, or stress.[54,55] However, using the DASS-21 we checked whether the group results could be explained by depression, anxiety, or stress. We found only one significant positive correlation between cortical thickness of the superior temporal gyrus and the depression scale score. The present results convincingly show the important involvement of the ventrolateral prefrontal regions in pain processing. It is noteworthy that we have also found changes in cortical thickness in other structures known to be associated with pain processing and modulation, including orbitofrontal regions, cingulate cortex, insula, and inferior parietal lobule. However, these regions did not survive Bonferroni correction.

Moreover, our results revealed that the pattern of specific alterations in brain morphology was directly related to the intensity of pain, i.e. the increase in cortical thickness of the pars opercularis of the inferior frontal gyrus corresponded to greater pain. Correlation analyses revealed that increased cortical thickness was related to higher pain intensity scores in the NSLBP group. Our result is consistent with a previous study of Schmidt-Wilcke et al. (2006) in patients with chronic back pain, whereby brain regions showing an increase in gray matter density (such as the left thalamus and left putamen) coincided with increasing pain intensity.[6]

Our findings of the relation between increased cortical thickness and increased pain scores in patients with NSLBP may reflect the consequence of a reorganization process of brain regions involved in a disproportionate amount of signals of pain, emotions, and cognition. We think that

this increased cortical thickness of the ventrolateral prefrontal cortex can eventually be normalized by specific and targeted training.[56] There is limited evidence available in the literature[57,58] showing that treating chronic pain with cognitive behavioral therapy can lead to alterations in prefrontal brain regions, and that the changes in these prefrontal regions correlate with clinical improvement. The question that morphological changes can be normalized needs to be addressed in further research.

Decreased cortical thickness in rostral anterior cingulate cortex: relationship with sensorimotor performance

The changes in morphology did not only correlate with pain scores, but also with functional changes in sensorimotor control. Our behavioral results revealed that the NSLBP group required significantly more time to perform the STSTS task on both stable and unstable support surface compared to the healthy controls. This result is in agreement with previous studies.[13,26] The STSTS task on unstable support surface is ultimately challenging the sensorimotor system (including the proprioceptive system), because this condition requires an additional reweighting of proprioceptive signals due to the decreased reliability of proprioceptive signals from the ankle region.[59] Proprioception can be defined as "the unconscious perception of movement and spatial orientation arising from stimuli within the body"[60] and the unstable support surface enforces the central nervous system to down-weight the less reliable ankle muscle proprioception, and consequently to up-weight the proprioceptive input from more proximal segments, in order to provide optimal postural control.[59,61] Nevertheless, a faster performance on unstable support surface compared to the stable condition was observed. Because of the non-randomized order of these conditions, this is possibly due to a learning effect. Despite this limitation, the individuals with NSLBP needed more time to perform five consecutive STSTS movements compared to controls, in both

conditions. This fits with previous findings.[13] The decreased performance on a sensorimotor task in individuals with NSLBP, as represented by the increased duration of the STSTS task, fits within the findings of previous studies showing impaired sensorimotor control in individuals with NSLBP.[10,62] Indeed the STSTS task requires optimal sensorimotor control, for example in terms of postural control.[63] Recently, an association was observed between the proprioceptive reweighting capacity and microstructural integrity of the superior cerebellar peduncle in individuals with NSLBP. This finding suggests a neural basis for sensorimotor impairments.[25] In this current study, the association between the sensorimotor STSTS task and structural morphometry in terms of cortical surface area and cortical thickness in individuals with NSLBP and healthy controls was investigated. Evaluation of these non-volumetric parameters as separate measures, reflecting different aspects of the underlying neural architecture, is of important interest to investigate what drives sensorimotor tasks.

In the present study, lower STSTS performance on unstable support surface was associated with decreased cortical thickness of the rostral anterior cingulate cortex. This correlation was significant within the total group and a trend within the group of the patients with NSLBP was found. The anterior cingulate cortex is considered as part of the general pain-matrix[64,65] and has been implicated in anticipation of pain and affective processing of pain.[66] Structural alterations in the anterior cingulate cortex have been reported in a wide range of chronic pain conditions.[46,47] The anterior cingulate cortex is also the brain region that most consistently shows activation in response to acute pain stimuli.[66] This is the first time that an association between the cortical thickness of the anterior cingulate cortex and performance on a sensorimotor task in individuals with NSLBP and healthy controls was observed.

Of note, our statistical analyses (group comparisons and correlation analyses) revealed only significance for cortical thickness. In light of the radial unit hypothesis[18,67], our significant cortical thickness findings may reflect abnormalities in the number of even size of the neuronal cell bodies within the cortical minicolumns of the ventrolateral prefrontal cortical regions in patients with NSLBP. In contrast, the absence of cortical surface area findings does not support that individuals with NSLBP may have abnormal proliferation or decline in the numbers of cortical minicolumns. However, the power of our study was probably not enough to detect a significant group difference in surface area. While our sample size was similar to prior studies investigating differences in brain structure in patients with chronic pain[46,47], we also performed post-hoc power analyses to determine whether negative findings for surface area could be attributed to the low sample size. We demonstrated that for the vast majority of the cortical parcellations, at least 41 subjects were required per group to observe significant differences in surface area. In order to precisely interpret these findings with respect to their functional significance further research addressing the relationship between cerebral micro- and macro- structures as well as brain function is clearly necessary.

Limitations

The main shortcoming of our study was the small sample size, especially for the numerous correlations performed from the Freesurfer output. Replication of the present morphological findings with a larger sample is warranted. Related to this, future studies in a large number of participants should also stratify the groups by age rather than controlling for age in the statistical analyses. Another limitation of the present study pertains to the correlative nature of our study. The correlation coefficients computed between the pain scores and brain morphometry provided us information about the nature of the relations between these variables, but did not allow tests of

strong causal inference. To achieve the latter, a longitudinal study is necessary. Finally, the inclusion of other dynamic sensorimotor tasks, such as gait, could further clarify the different aspects of sensorimotor control.

Conclusion

In the present study, patients with NSLBP showed alterations of cortical thickness in brain regions that play an important role in the cognitive regulation of pain, as well as an impaired STSTS performance compared to healthy controls. Cortical thickening was associated with increased pain intensity in the individuals with NSLBP. In addition, lower STSTS performance on unstable support surface was correlated with decreased cortical thickness of the rostral anterior cingulate cortex. These findings suggest that in addition to measures of volume, cortical thickness may provide a more complete understanding of the central basis of sensorimotor tasks, more specifically in the NSBLP population.

FIGURE LEGENDS

Figure 1. Significant group differences (after correcting for age) in cortical thickness.

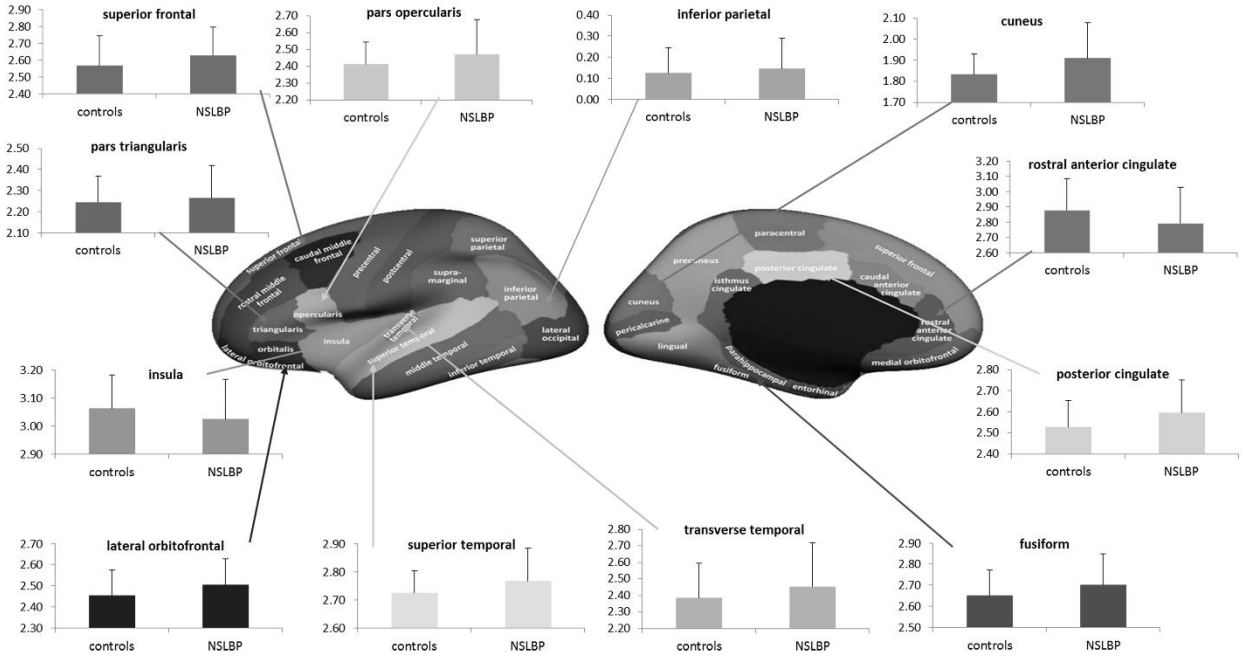

Figure 2. Scatter plots indicating the relationship between cortical thickness and STSTS performance and pain intensity score.

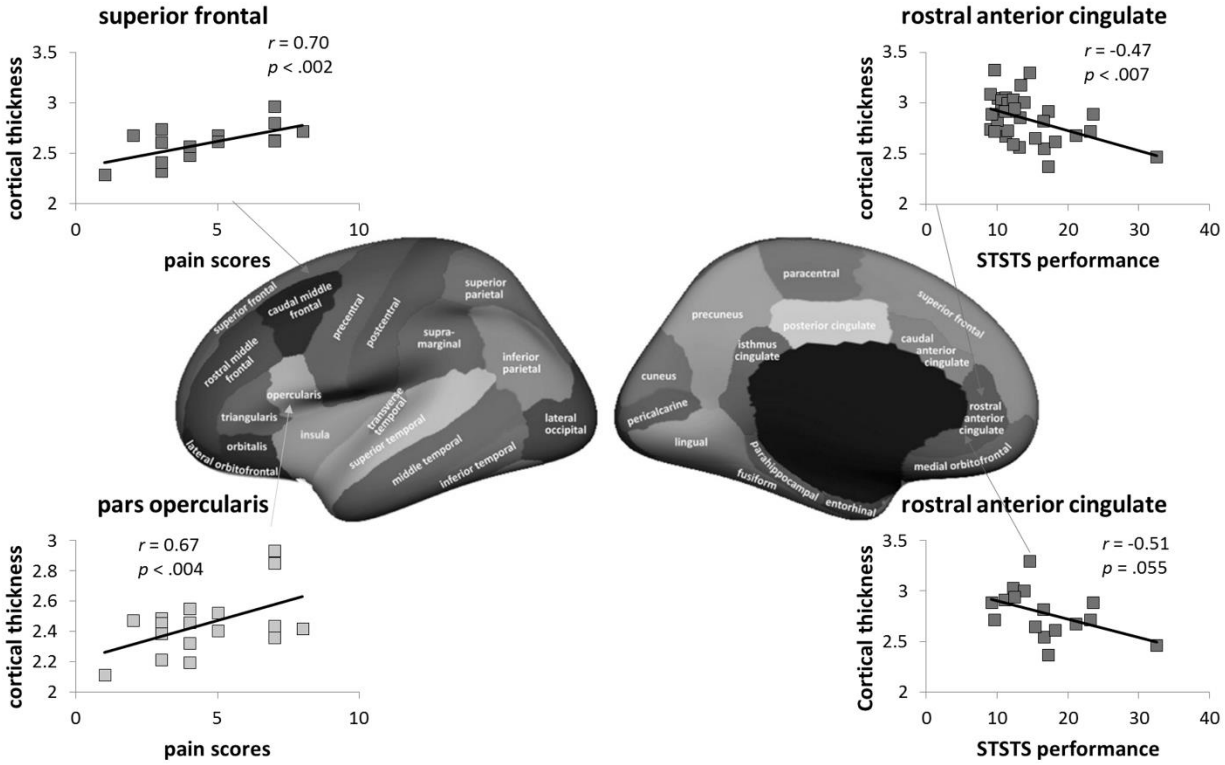

Table 1. Characteristics of the participants

Characteristic	**NSLBP group (n= 17)**	**Healthy group (n= 17)**	**p-value**
Age (years)	33.3 ± 7.9	31.8 ± 8.2	NS
Gender (male/female)	6/11	5/12	NS
Height (cm)	173.0 ± 6.4	169.1 ± 6.4	NS
Weight (kg)	72.7 ± 10.6	64.9 ± 10.2	p= 0.036
BMI (kg/m^2)	24.2 ± 2.8	22.6 ± 2.7	NS
ODI-2	20.6 ± 7.6	0	N/A
NSLBP duration (years)	9.8 ± 8.2	0	N/A
NRS$_{back}$ usual	4.5 ± 2.0	0	N/A
NRS$_{back}$ current	2.0 ± 2.0	0	N/A

Data are presented as mean ± standard deviation. NSLBP: non-specific low back pain; BMI: body mass index; ODI-2: Oswestry Disability Index, version 2 (adapted Dutch version); NRS$_{back}$ usual: back pain score on the numerical rating scale (0-10) during the last month; NRS$_{back}$ current: back pain score on the numerical rating scale (0-10) at the moment of testing; significance level ($p < 0.05$); N/A: not applicable.

Table 2. Relationships between weight and measures of pain.

Measure of pain	Spearman correlation coefficient	p- value
NPRS back last month	0.314	0.071
NPRS back at the moment of testing prior to completion of test	0.303	0.082
Years of NSLBP	0.357	0.038
Amount of episodes of NSLBP	0.323	0.065

Table 3: Cortical thickness values per group.

Cortical thickness	Healthy controls		NSLBP		Corrected for age	
Cortical parcellation	Average	SD	Average	SD	F	Sig. (p)
Bank ssts	2.357	0.120	2.394	0.124	1.004	.381
Caudal anterior cingulate	2.536	0.210	2.676	0.178	2.716	.086
Caudal middle frontal	2.319	0.155	2.394	0.203	2.919	.073
Cuneus	1.832	0.098	1.910	0.168	7.183	*.003*
Entorhinal	3.357	0.243	3.402	0.273	.100	.905
Fusiform	2.652	0.120	2.701	0.147	6.896	*.004*
Inferior parietal	2.296	0.124	2.388	0.144	7.830	*.002*
Inferior temporal	2.514	0.091	2.504	0.116	1.281	.295
Isthmus cingulate	2.571	0.194	2.613	0.136	2.511	.101
Lateral occipital	2.049	0.133	2.102	0.123	3.784	.037
Lateral orbitofrontal	2.455	0.120	2.503	0.124	6.951	*.004*
Lingual	2.086	0.130	2.120	0.126	4.933	.016
Medial orbitofrontal	2.301	0.159	2.312	0.149	.501	.612
Middle temporal	2.629	0.141	2.663	0.088	3.720	.039
Parahippocampal	2.871	0.372	2.816	0.293	.713	.500
Paracentral	2.290	0.157	2.371	0.169	2.466	.105
Pars opercularis	2.411	0.133	2.469	0.206	14.459	**.000**
Pars orbitalis	2.388	0.147	2.472	0.177	1.300	.290
Pars triangularis	2.245	0.124	2.264	0.156	9.951	**.001**
Pericalcarine	1.534	0.116	1.596	0.153	1.268	.299
Postcentral	1.913	0.103	1.994	0.141	4.735	.018
Posterior cingulate	2.528	0.126	2.596	0.155	5.858	*.008*
Precentral	2.426	0.189	2.467	0.169	4.526	.021
Precuneus	2.350	0.167	2.418	0.172	1.811	.184
Rostral anterior cingulate	2.875	0.208	2.791	0.236	5.745	*.009*
Rostral middle frontal	2.086	0.119	2.158	0.148	3.172	.059
Superior frontal	2.565	0.178	2.625	0.169	5.549	*.010*
Superior parietal	2.000	0.140	2.108	0.172	3.637	.041
Superior temporal	2.725	0.079	2.766	0.118	6.283	*.006*
Supramarginal	2.374	0.118	2.424	0.122	5.079	.014
Frontal pole	2.461	0.295	2.597	0.229	2.169	.135
Temporal pole	3.613	0.232	3.623	0.243	.008	.992

Transverse temporal	2.383	0.212	2.450	0.270	7.129	*.004*
Insula	3.062	0.119	3.023	0.143	7.940	*.002*

Table 4: Cortical surface area values per group.

Surface area	Healthy controls		NSLBP		Corrected for age		Required sample size
Cortical parcellation	Average	SD	Average	SD	F	Sig. (p)	
Bank ssts	904	139	982	138	0.651	0.534	51
Caudal anterior cingulate	705	119	664	79	1.152	0.339	96
Caudal middle frontal	2241	251	2182	215	0.316	0.733	249
Cuneus	1463	171	1473	135	0.633	0.543	3637
Entorhinal	324	73	343	55	0.598	0.561	186
Fusiform	3098	432	3196	337	0.317	0.733	247
Inferior parietal	4969	525	4909	358	0.126	0.883	885
Inferior temporal	3095	461	3170	290	0.133	0.876	411
Isthmus cingulate	918	173	889	134	0.246	0.785	460
Lateral occipital	4716	638	4535	498	0.949	0.407	158
Lateral orbitofrontal	2383	279	2398	260	0.103	0.902	4991
Lingual	3075	343	3007	391	0.402	0.675	454
Medial orbitofrontal	1645	178	1682	162	0.167	0.847	348
Middle temporal	3191	344	3109	331	0.221	0.804	266
Parahippocampal	677	84	703	64	1.234	0.316	126
Paracentral	1387	118	1404	142	1.011	0.385	989
Pars opercularis	1483	206	1446	206	0.138	0.872	498
Pars orbitalis	666	77	680	83	0.183	0.835	533
Pars triangularis	1325	117	1322	159	3.348	0.059	29790
Pericalcarine	1308	175	1303	101	0.111	0.895	11984
Postcentral	3895	445	4179	460	1.801	0.195	41
Posterior cingulate	1170	189	1188	118	1.589	0.233	1220
Precentral	4488	492	4789	478	1.838	0.189	42
Precuneus	3866	511	3766	337	0.422	0.662	293
Rostral anterior cingulate	718	94	744	81	0.391	0.682	178
Rostral middle frontal	5537	731	5495	548	0.024	0.977	3694
Superior frontal	6748	783	7040	588	1.155	0.338	90
Superior parietal	5363	373	5202	324	0.735	0.494	76
Superior temporal	3589	277	3622	310	0.135	0.874	1300
Supramarginal	3700	442	3594	453	0.616	0.552	283
Frontal pole	252	27	236	25	1.922	0.177	47

Temporal pole	445	69	439	45	0.046	0.955	1428
Transverse temporal	398	48	401	43	1.570	0.237	3362
Insula	1963	175	2006	168	0.299	0.745	248

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